Malaria Prevention in Travelers 2006

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Acknowledgement:

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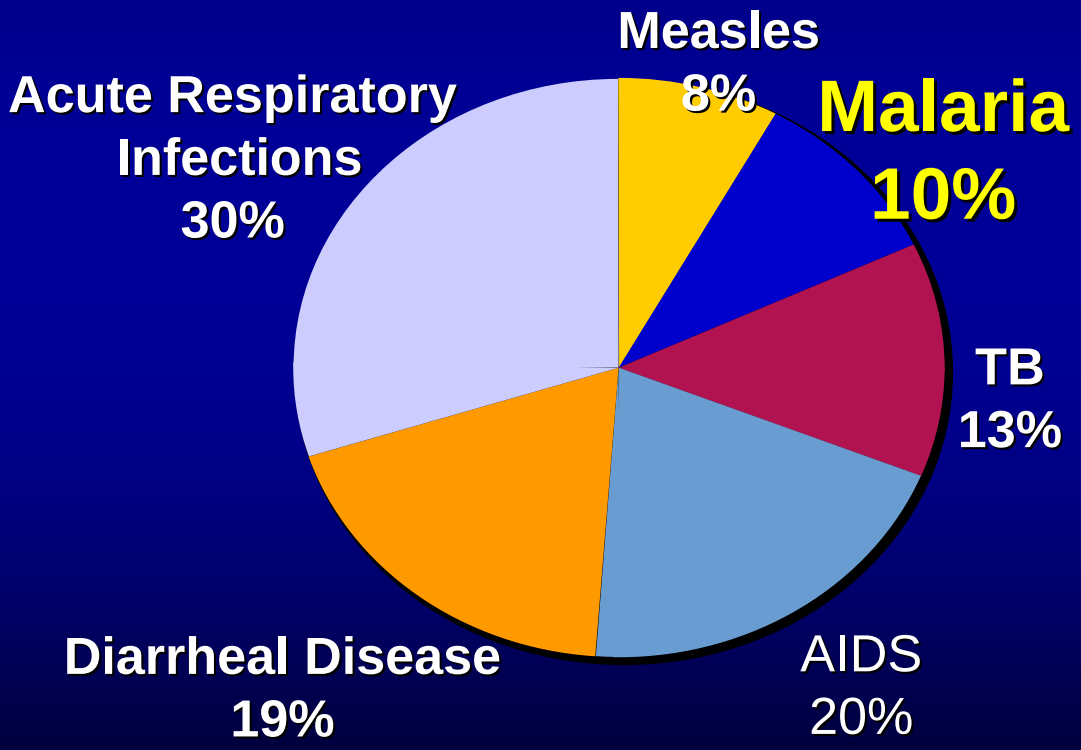
Professor of Medicine
University of Toronto, Canada

World's Most Important Parasitic Disease Is Malaria

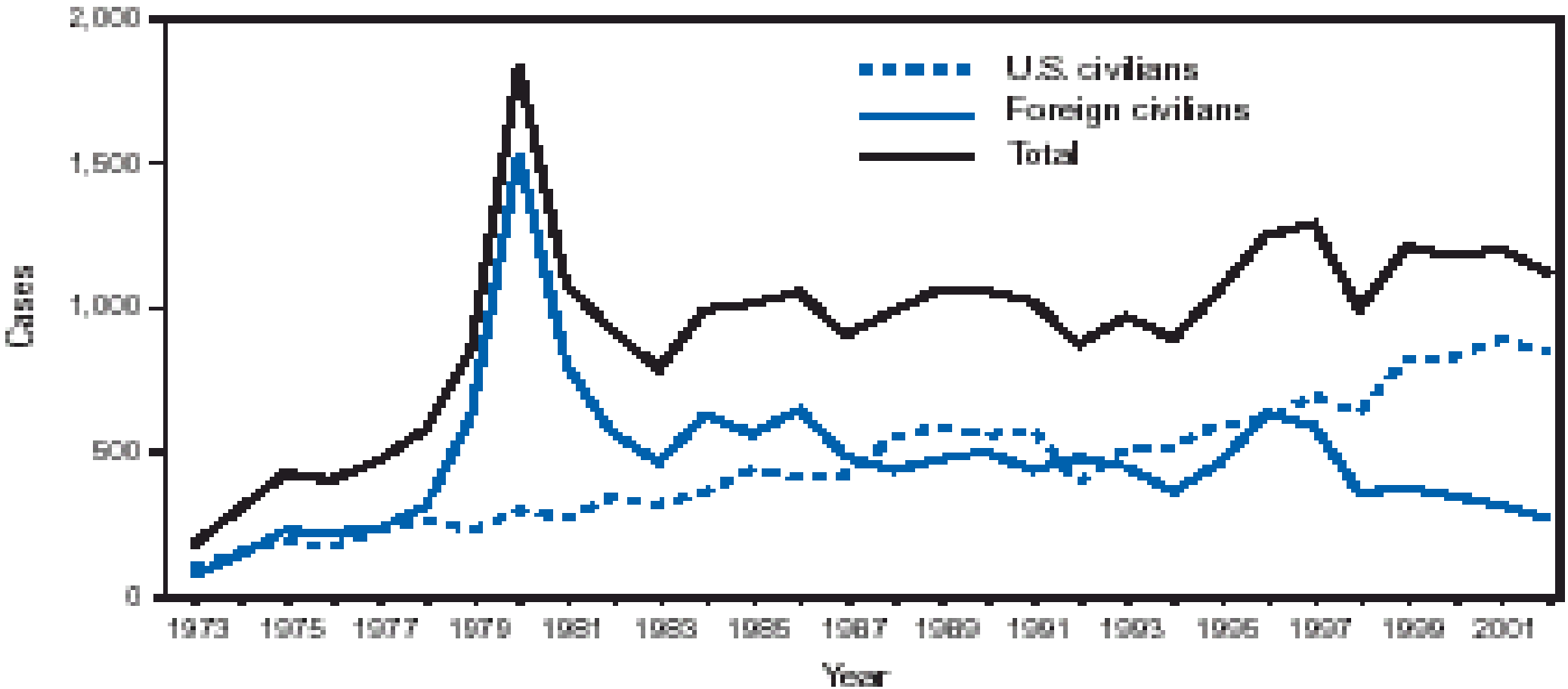
Deaths caused by leading infectious diseases in 1998[2]



- 300 to 500 million cases of malaria reported each year[1]
- 1.1 million deaths in 1998, compared with 2.3 million from AIDS[2]

[1]Taylor TE, Strickland GT. Infections of the blood and reticuloendothelial system. In: Strickland GT, ed. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. 8th ed. Philadelphia, Pa: W.B. Saunders Company; 2000: 614-643.
[2]World Health Organization. 1999 Infectious Diseases Report. Graph 5. Available at: http://www.who.int/infectious-disease-report/pages/graph5.html. Accessed May 23, 2002.

FIGURE 1. Number of malaria cases among U.S. and foreign civilains — United States,* 1973–2002†



* Includes Puerto Rico, Guam, and the U.S. Virgin Islands.
† The substantial increase in the number of cases reported for 1980 primarily reflects cases diagnosed among immigrants from Southeast Asia.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 12, 2006 VOL. 354 NO. 2

Spectrum of Disease and Relation to Place of Exposure among Ill Returned Travelers

David O. Freedman, M.D., Leisa H. Weld, Ph.D., Phyllis E. Kozarsky, M.D., Tamara Fisk, M.D.,*
Rachel Robins, M.D., Frank von Sonnenburg, M.D., Jay S. Keystone, M.D., Prativa Pandey, M.D.,
and Martin S. Cetron, M.D., for the GeoSentinel Surveillance Network†

Imported malaria USA 2003

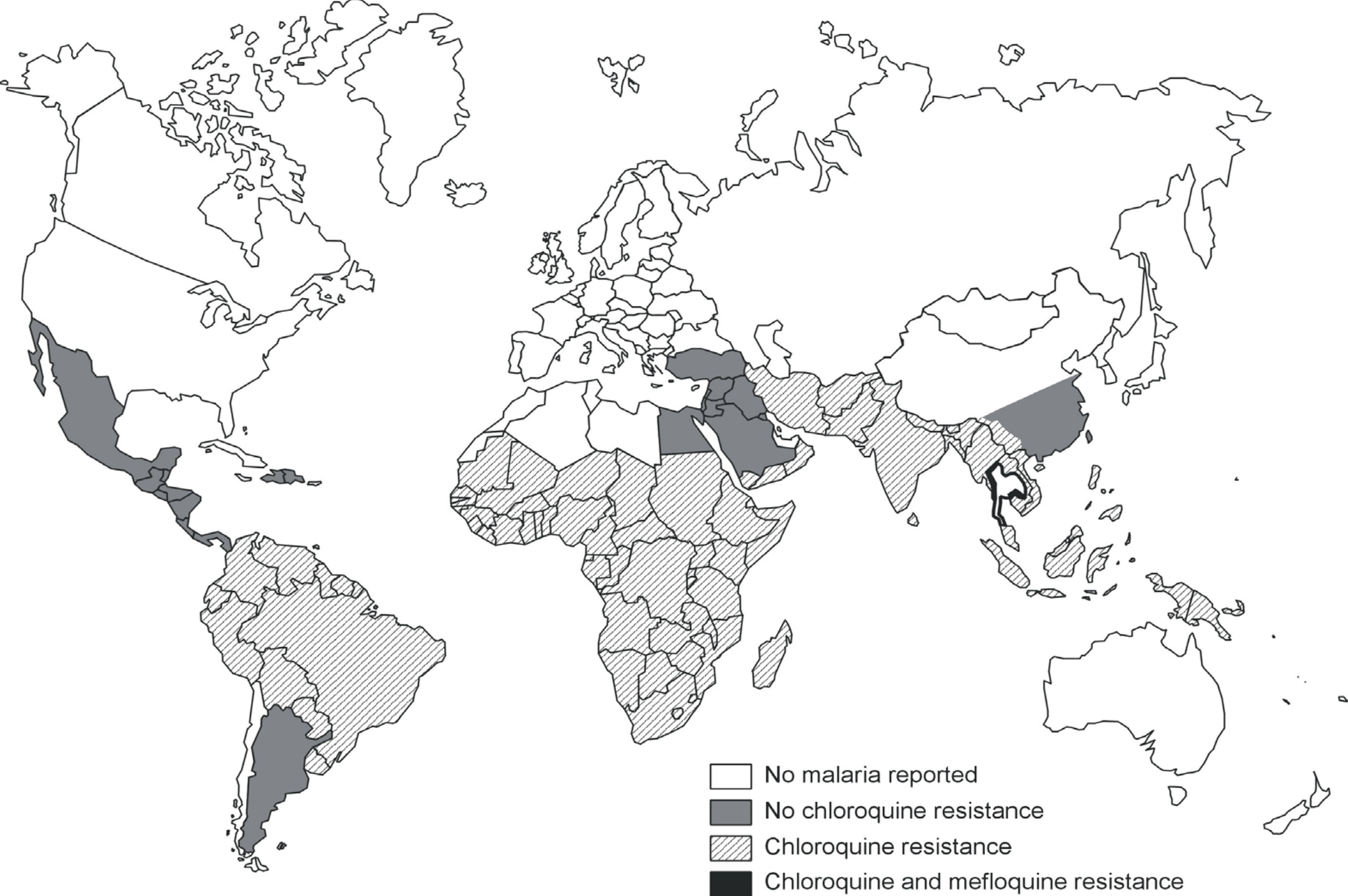
N= 783 MMWR 2005;54:25-39

Category	Percent
VFRs	53.9
Tourism	12.5
Missionary	9.2
Business	7.5
Student	3.8

Percent Fever in Returned Travelers

N=3907 NEJM 2005;354:

Etiology	Carib	CAm	SAm	SSA	SA	SEA
malaria	<1	13	13	62	14	13
dengue	23	12	14	<1	14	32
mono	7	7	8	1	2	3
rickettsia	0	0	0	6	1	2
Salmon.	2	3	2	<1	14	3


No malaria reported
No chloroquine resistance
Chloroquine resistance
Chloroquine and mefloquine resistance

Malaria chemoprophylaxis considerations

1. Is the traveler going to a malarious area?
2. Will the traveler be *exposed* to malaria?
3. Is the area chloroquine or mefloquine resistant?
4. Are there any contraindications to antimalarial use (pregnancy, cost etc) ?

Malaria chemoprophylaxis considerations

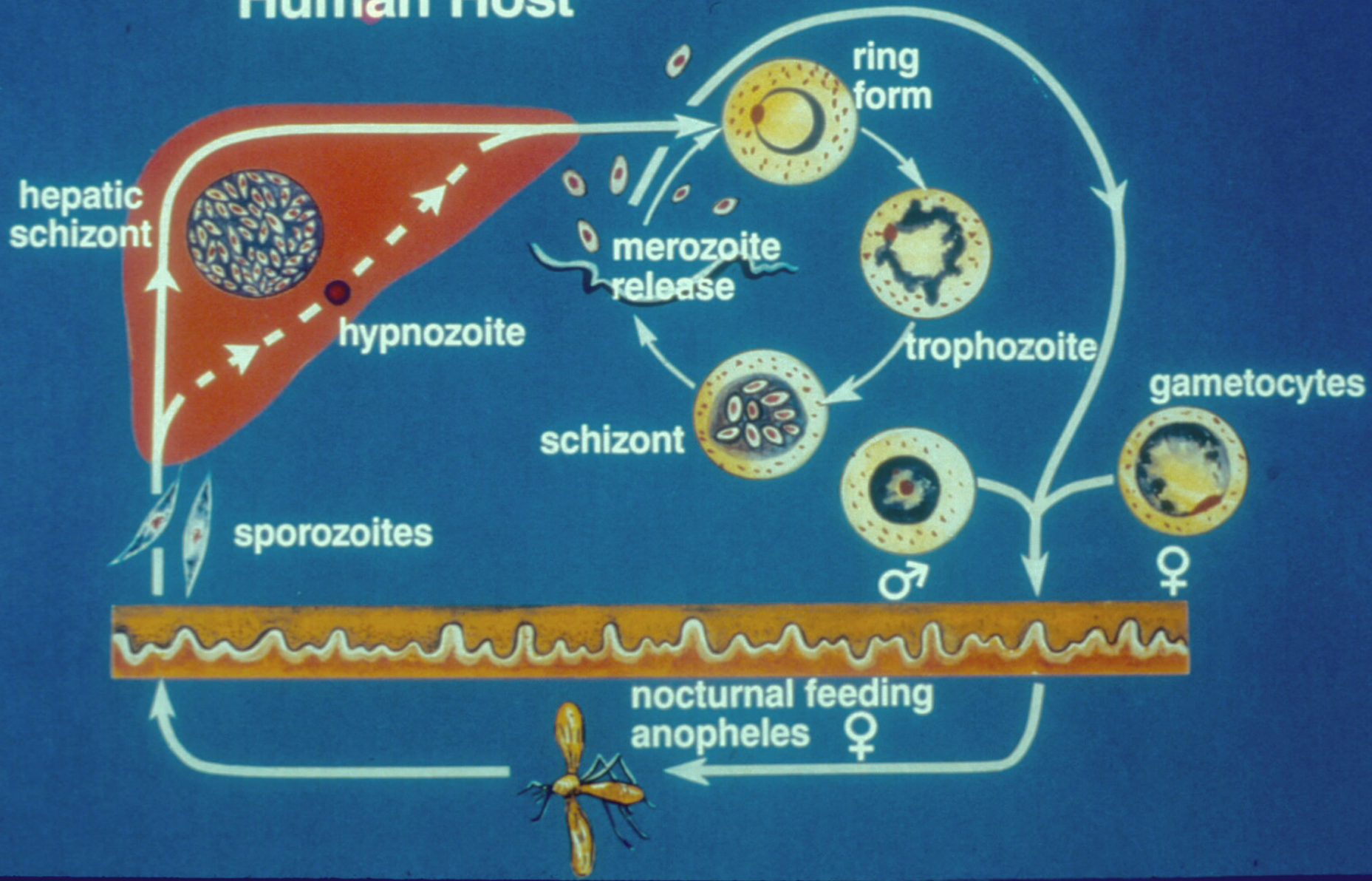
5. What is travelers experience with antimalarials?
6. What is the duration of antimalarial use?
7. Is there any indication for presumptive self-tx?

Drug Resistant malaria

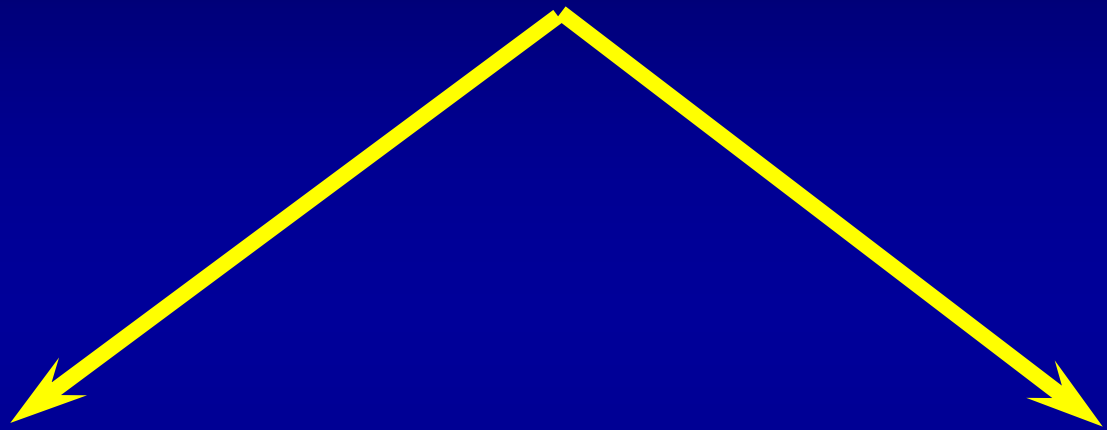
- Chloroquine sensitive *P. falciparum*
- Chloroquine resistant *P. falciparum*
- Mefloquine resistant *P. falciparum*
- Chloroquine resistant *P. vivax, malariae*
- Primaquine tolerant *P. vivax*

Life Cycle of Malaria

Human Host



Prevention of malaria



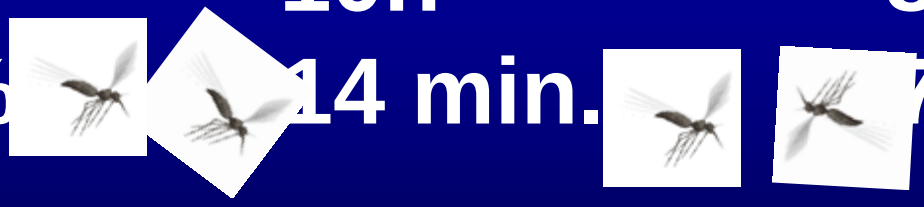
personal protection measures

antimalarials

Personal Protective Measures

Relative Duration of Action of Insect Repellents

Ingredient	mean	range
DEET 5%	1h	0.75 2h
DEET 23%	5h	3.5 – 6h
DEET 99%	10h	8 - 12h
Citronella 10%	14 min.	7 – 60m



*Except: ultrathon & Sawyer CR DEET: 20-30%= 10-12 hr

Fradin NEJM 2002:347:13-18

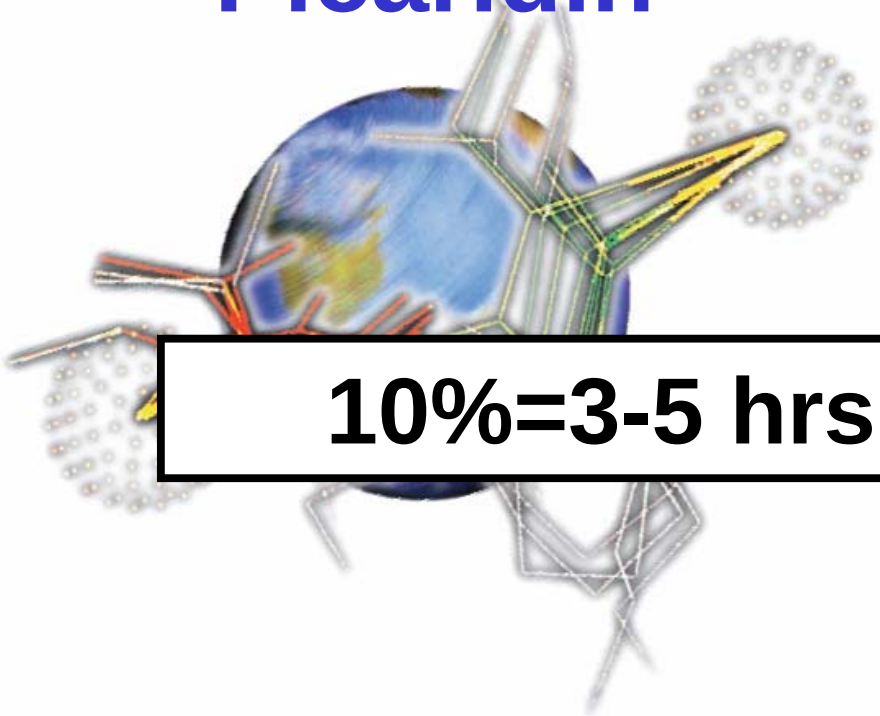
Optimum combination = 99.99% protection

DEET (skin) + Permethrin (clothing)

Bayrepel®

The new active ingredient in AUTAN®

Picaridin



10%=3-5 hrs. 20%= 8-10hrs

AUTAN®

Bayer

DEET use in Children

DEET recommendations 2003:

EPA and AAP:

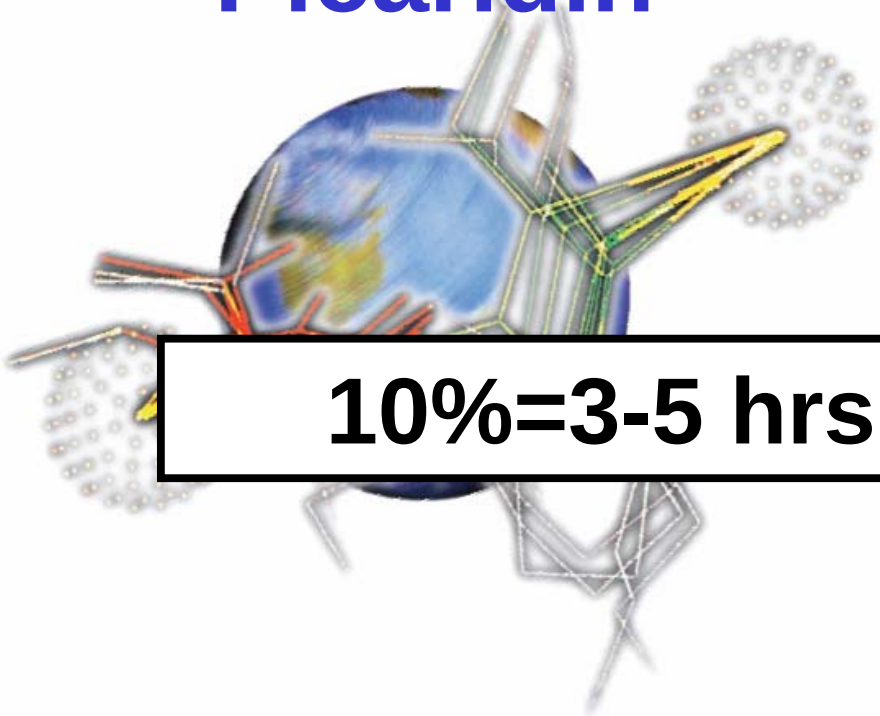
30% DEET safe in children:

≥ age 2 months of age

Bayrepel®

The new active ingredient in AUTAN®

Picaridin



10%=3-5 hrs. 20%= 8-10hrs

AUTAN®

Bayer

Safety of DEET in pregnancy

McGready, Am J Trop Med 2001;65:285-89

- Thai study, RCT, DEET vs. control
- 450 women/grp - 2nd & 3rd trimester
- use of DET over 18 wks
- 200 gm DEET total = 1 litre of 20% DEET
- 597/741 births followed x 1 yr.

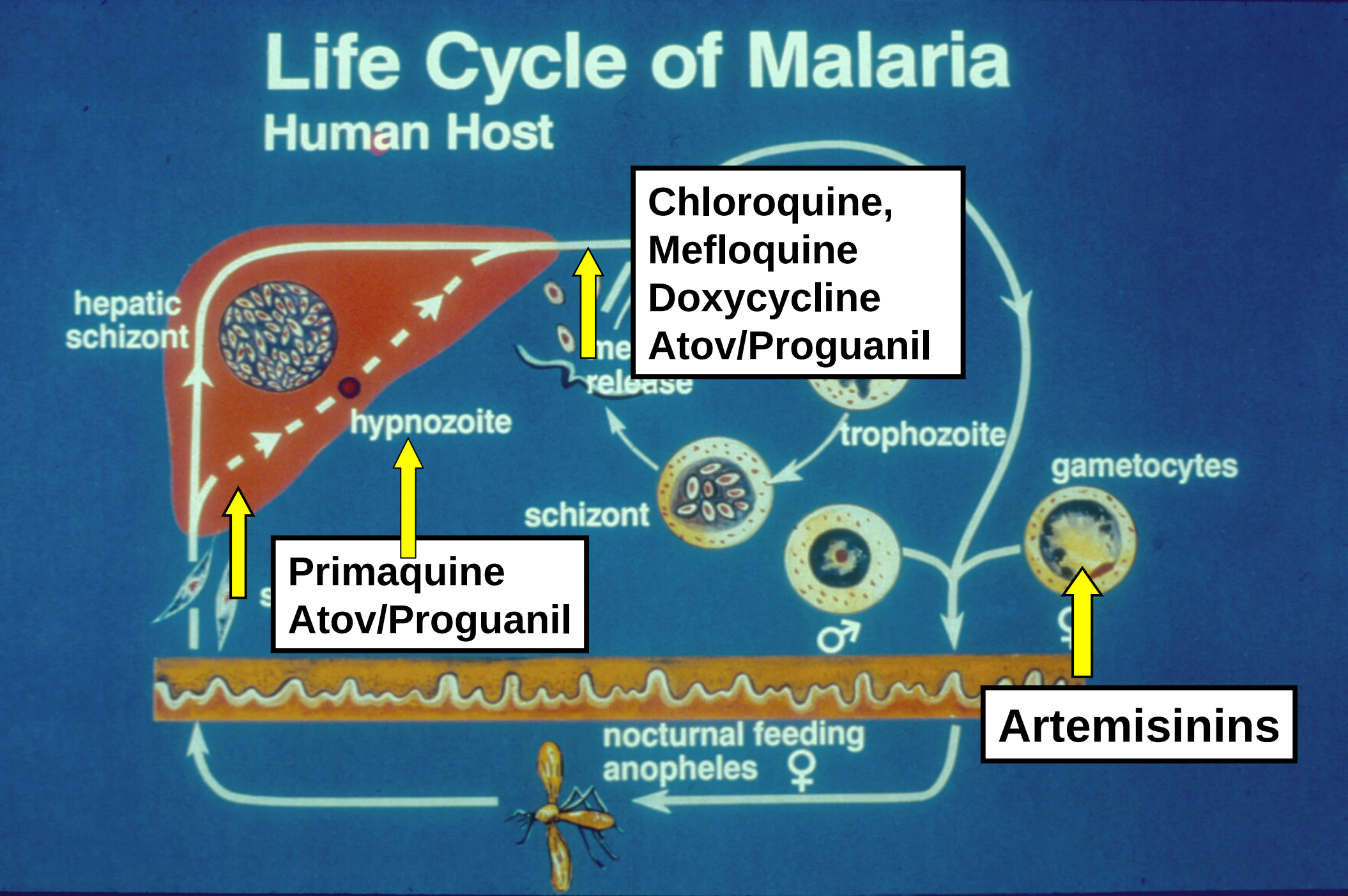
Safety of DEET in pregnancy (Cont'd.)

1. DEET detection:
   - 0/30 samples in urine
   - 4/50 samples of cord blood
2. Birth outcomes: no difference both groups
   - neurological exam
   - growth parameters
   - congenital abnormalities (6 variable)
   - survival @ birth & 1 year
   - developmental delay

Optimum combination = 99.99% protection

DEET (skin) + Permethrin (clothing)

Prophylaxis with Antimalarials


Life Cycle of Malaria
Human Host
hepatic schizont
hypnozoite
release
trophozoite
schizont
gametocytes
nocturnal feeding anopheles ♀
Chloroquine,
Mefloquine
Doxycycline
Atov/Proguanil
Primaquine
Atov/Proguanil
Artemisinins

Malaria Chemoprophylaxis

Chloroquine Sensitive malaria: 😐

chloroquine

Chloroquine Resistant Malaria ☹

mefloquine

DOC { doxycycline
atovaquone/proguanil
primaquine

Chloroquine

- 4-aminoquinolone
- Reduced efficacy globally to *P.falciparum*
- 500 mg weekly beginning 1-2 weeks prior and 4 weeks after exposure
- GI upset, keratopathy ,
- pruritus in African Americans
- Safe in pregnancy

Drugs for Chloroquine Resistant Malaria

Drug	Advantage	Disadvantage
Mefloquine *Lariam*	Weekly Moderate cost $$	Neuropsychiatric Adverse Drug Reactions (ADR) 1-2 wks pre;4 wks post

Now hear this…..the M word!

If you prescribe mefloquine without discussing adverse events *and* alternative chemoprophylactic agents, you will likely meet ….

Am. J. Trop. Med. Hyg., 65(3), 2001, pp. 189–192

SERIOUS ADVERSE EVENTS OF MEFLOQUINE IN RELATION TO BLOOD LEVEL AND GENDER

ELI SCHWARTZ, ISRAEL POTASMAN, MICHAL ROTENBERG, SHLOMO ALMOG, AND SIEGAL SADETZKI

Center for Geographic Medicine, Laboratory of Clinical Pharmacology and Toxicology, and Department of Clinical Epidemiology, Sheba Medical Center, Tel-Hashomer, Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel; Infectious Diseases Unit, Bnai Zion Medical Center, Haifa, Israel

Abstract. Mefloquine is widely used for prophylaxis in areas with chloroquine-resistant falciparum malaria. As the use of mefloquine has increased, so have the reports on its adverse effects. We sought to evaluate the possible association between serum levels of mefloquine and serious side effects caused by this drug by means of a case-control design study. The study population included 17 patients who presented to emergency rooms or travel clinics with symptoms suggesting serious adverse effects of mefloquine and 28 controls (healthy people, still taking mefloquine after travel). The mean age of the patients and the controls was 31.5 ± 11.6 years and 34 ± 12.2 years, respectively. The percentage of women among the patients was higher than in the control population (76% versus 40%, patients interr as found between the patients and the control groups. Also, no significant difference was found between mefloquine levels in

Women have more ADR's than men

No correlation between ADR's and drug levels

Mefloquine (Lariam®)

- Most adverse effects 1-3rd dose
- start 4 weeks before exposure or loading dose :1 tab daily x 3 days then weekly thereafter

Curses, Madness, and Mefloquine

OLADIPO KUKOYI, M.D.
CAROLINE P. CARNEY, M.D., M.SC.

Mefloquine is a quinoline-methanol compound structurally similar to quinine. Because of its efficacy and once-weekly dosing, mefloquine is a good choice for malaria prophylaxis for travelers to areas with chloroquine-resistant *Plasmodium falciparum* malaria. It is recommended as the drug of choice by most authorities.[1] It has a wide volume of distribution, can cross the blood-brain barrier, has a half-life of [illegible] such as [illegible] (desc[illegible] effects. Mefloquine has rarely been linked to more severe mental status changes such as psychosis.[3–5] This report presents the case of a young woman who developed severe psychosis after re-exposure to mefloquine and whose treatment was complicated by sociocultural issues.

Tolerance to mefloquine once does not mean tolerance to the drug the second time

vinced that her husband was the Devil. She started to eat from garbage cans, as she believed her food was being poisoned.

Her husband's emigration to the United States was considered a sign of success in his home community. It was proposed by her in-laws that people jealous of his success had cast a spell on his wife to drive her insane. The [illegible] prayer and fasting commenced. After several days without improvement in his wife's symptoms, Ms. A's husband surreptitiously took her and their 3-year-old daughter and boarded a flight back to the United States. The alleged culprit who had cast the spell had been identified, and he wanted to get as far away from her as possible. On the

Drugs for Chloroquine Resistant Malaria

Drug	Advantage	Disadvantage
Doxycycline	Lowest cost $	Daily; sun burn*; GI; vaginal yeast infection ☹ 1day pre,4 wks post (fluconazole) ☹

Sunburn: 5-15%

Drugs for Chloroquine Resistant Malaria

Drug	Advantage	Disadvantage
Malarone *Atovaquone /proguanil*	Safety Convenience 1 day pre;7 days post	Highest Cost $$$ headache, GI upset, insomnia; Daily?

Tolerability of antimalarials: RDB 4 arm study % Neuropsychological AE's*

Schlagenhauf BMJ 2003;327:1078

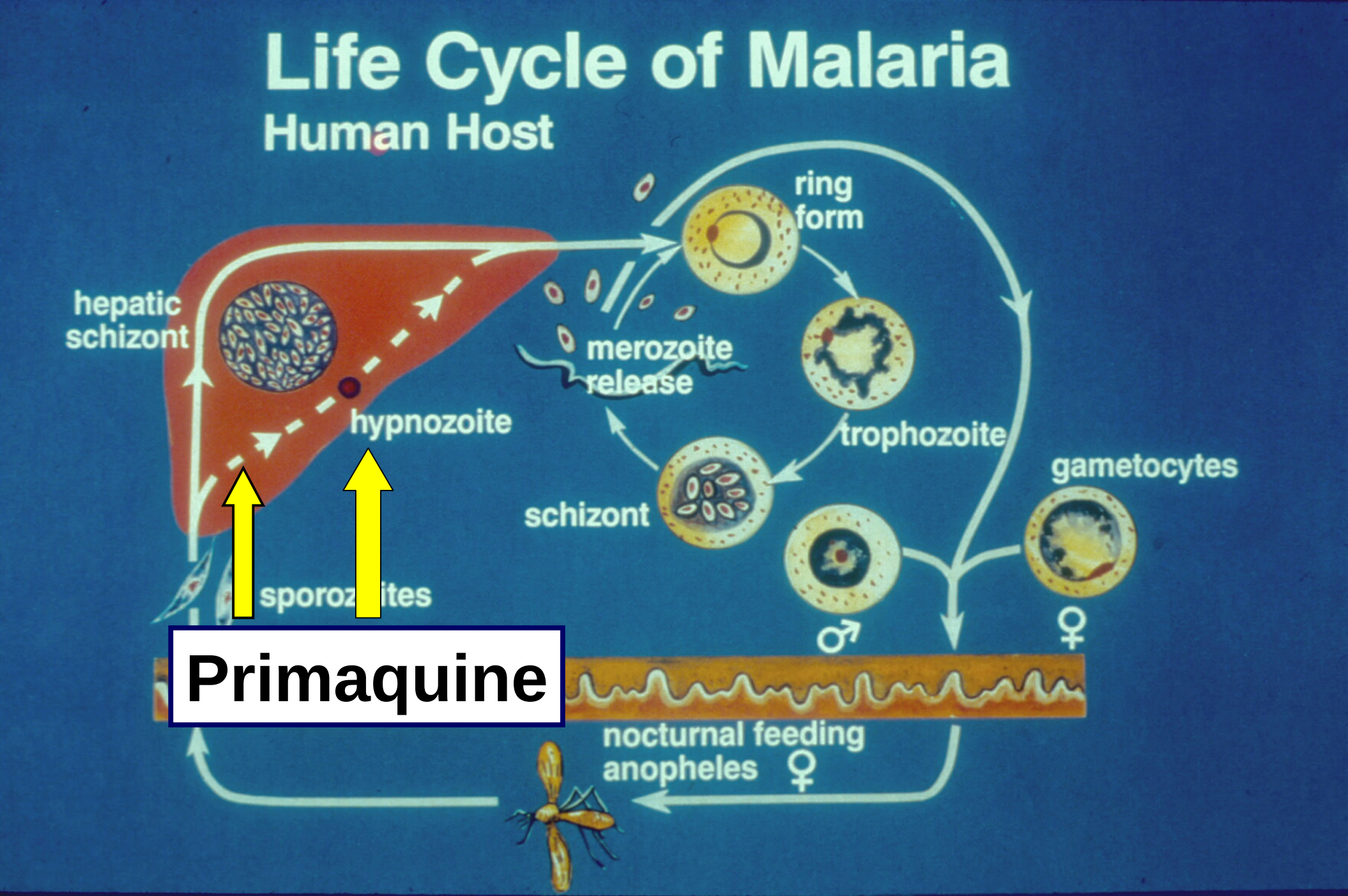
Adverse event	Mefloquine N=153	Doxycycline N=153	Atov/prog N=154
severe	5	1	3
moderate	37	24	20
all events	77	69	67

*headache, vivid dreams, dizziness, depression, anxiety, insomnia

Drugs for Chloroquine Resistant Malaria

Drug	Advantage	Disadvantage
Primaquine	Low cost $$ 1 day pre; 3 days post	*G6PD level required Daily; take with food

*Off label


Life Cycle of Malaria
Human Host
ring form
hepatic schizont
merozoite release
hypnozoite
trophozoite
schizont
gametocytes
sporozoites
Primaquine
nocturnal feeding anopheles ♀

Primaquine Prophylaxis

- 8-aminoquinolone
- tissue schizonticide → causal prophylaxis
- **Dose:** 30 mg (base) = 2 tabs/day, 1 day before and 3 days after exposure
- **Efficacy:** 85-95% (Pf + Pv) in 3 studies:

Irian Jaya, Kenya & Colombia

Primaquine Prophylaxis in non-immunes

	Fryauff	Soto	Baird
Duration (weeks)	52	16-18	20
No. in primaquine group	43	122	97
P.Falciparum PE (95%CI)	94 (61-99)	94 (78-99)	88 (48-97)
P.Vivax PE (95%CI)	90 (65-99)	84 (57-96)	92 (37-99)
All malaria PE (95%CI)	92 (77-99)	89 (75-96)	93 (71-98)

Primaquine Prophylaxis
Cont'd.

- **Adverse events:** GI upset, met Hb
- **C/I:** G6PD deficiency, pregnancy
- **Helpful hints:** G6PD screen, take with food

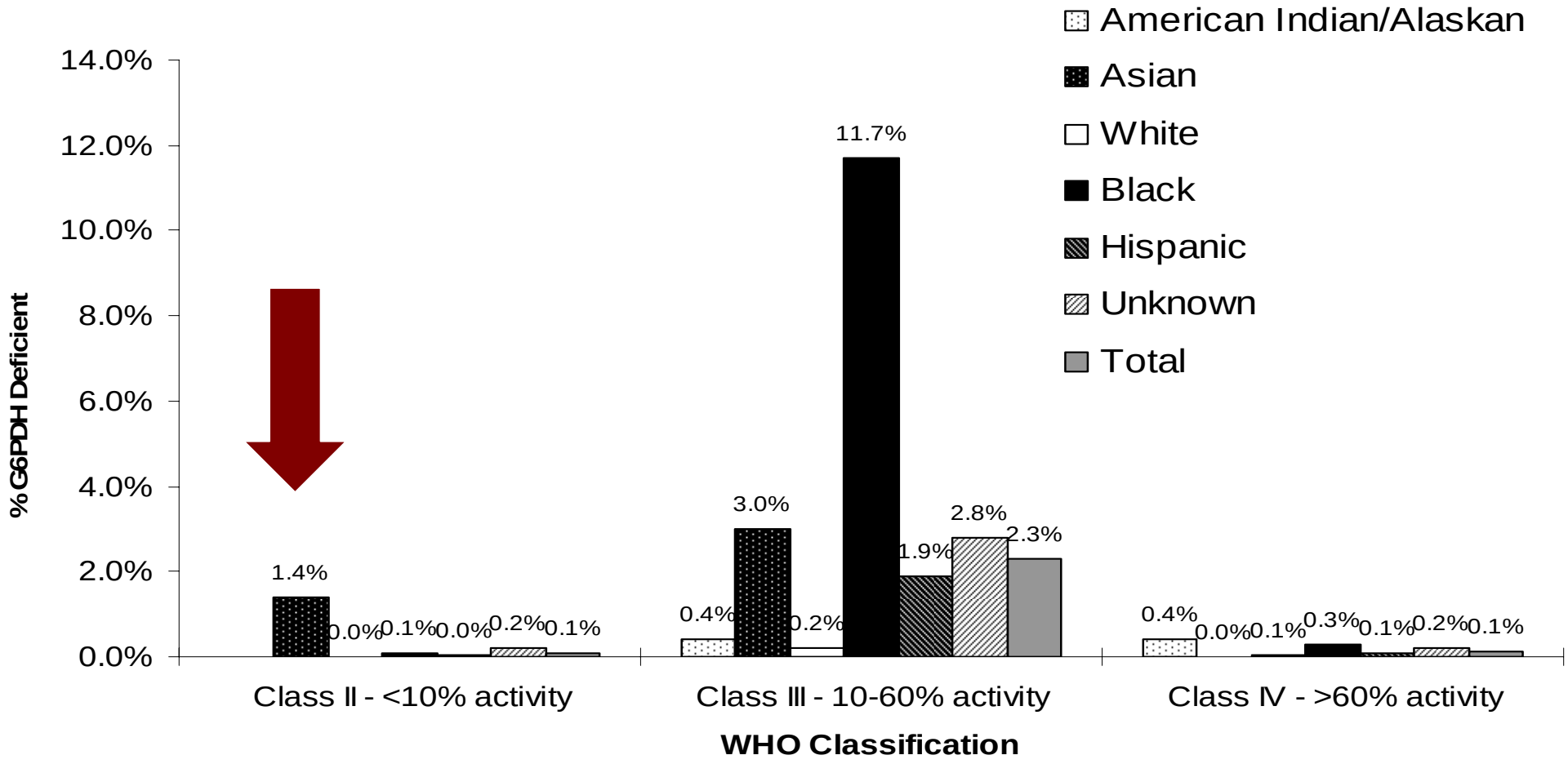
Soto, Ann Int Med 1998; 129:241,
Fryauff, Lancet 1995;346:1190

Percent G6PD deficiency in US military personnel

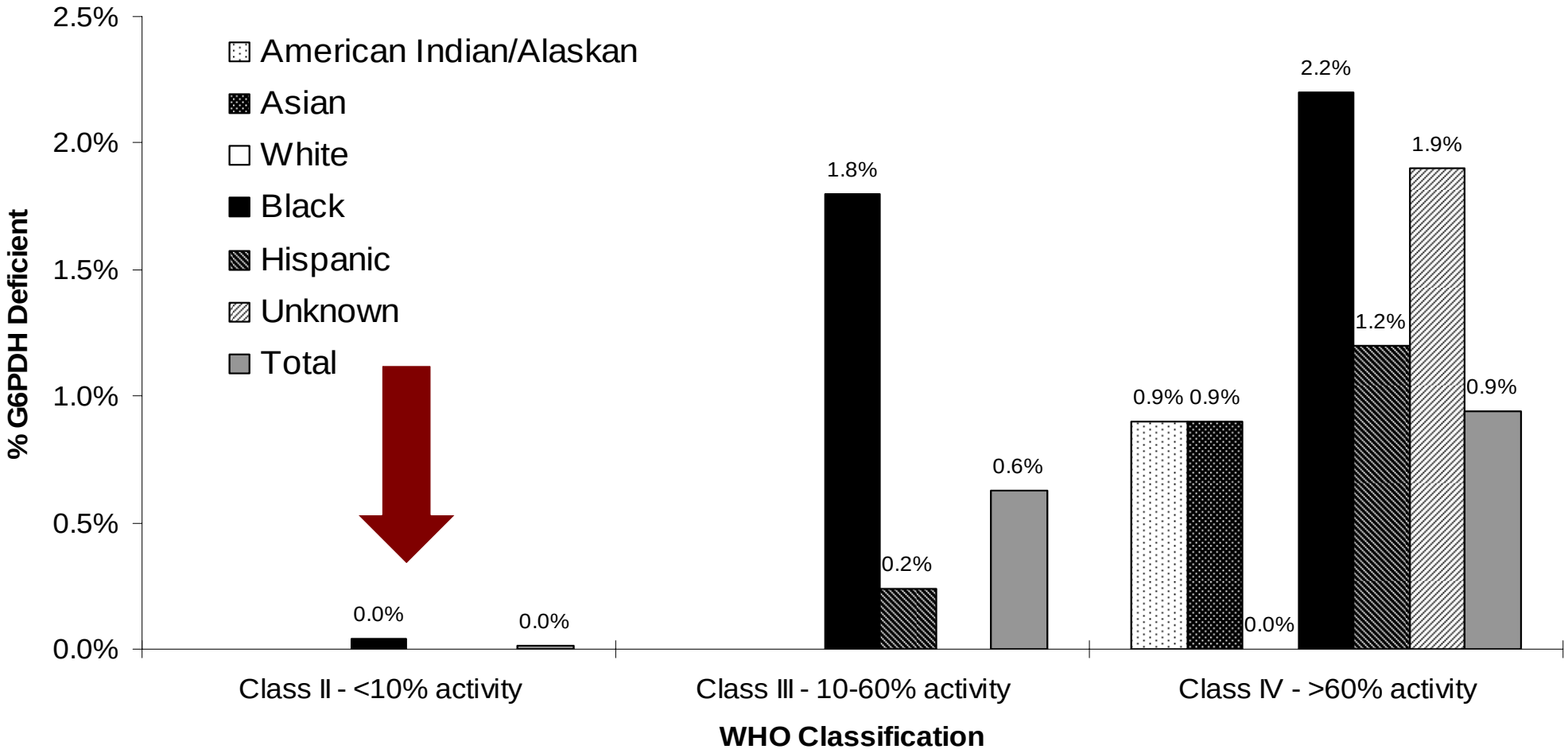
Ethnicity	*NO.*	*F*	*M*	*Total*
Native American	604	0.9	0.8	0.8
Asian	2123	0.9	4.3	3.6
Black	11,276	4.1	12.2	10.2
Hispanic	5304	1.2	2.0	1.9
White	42,162	0.0	0.3	0.3

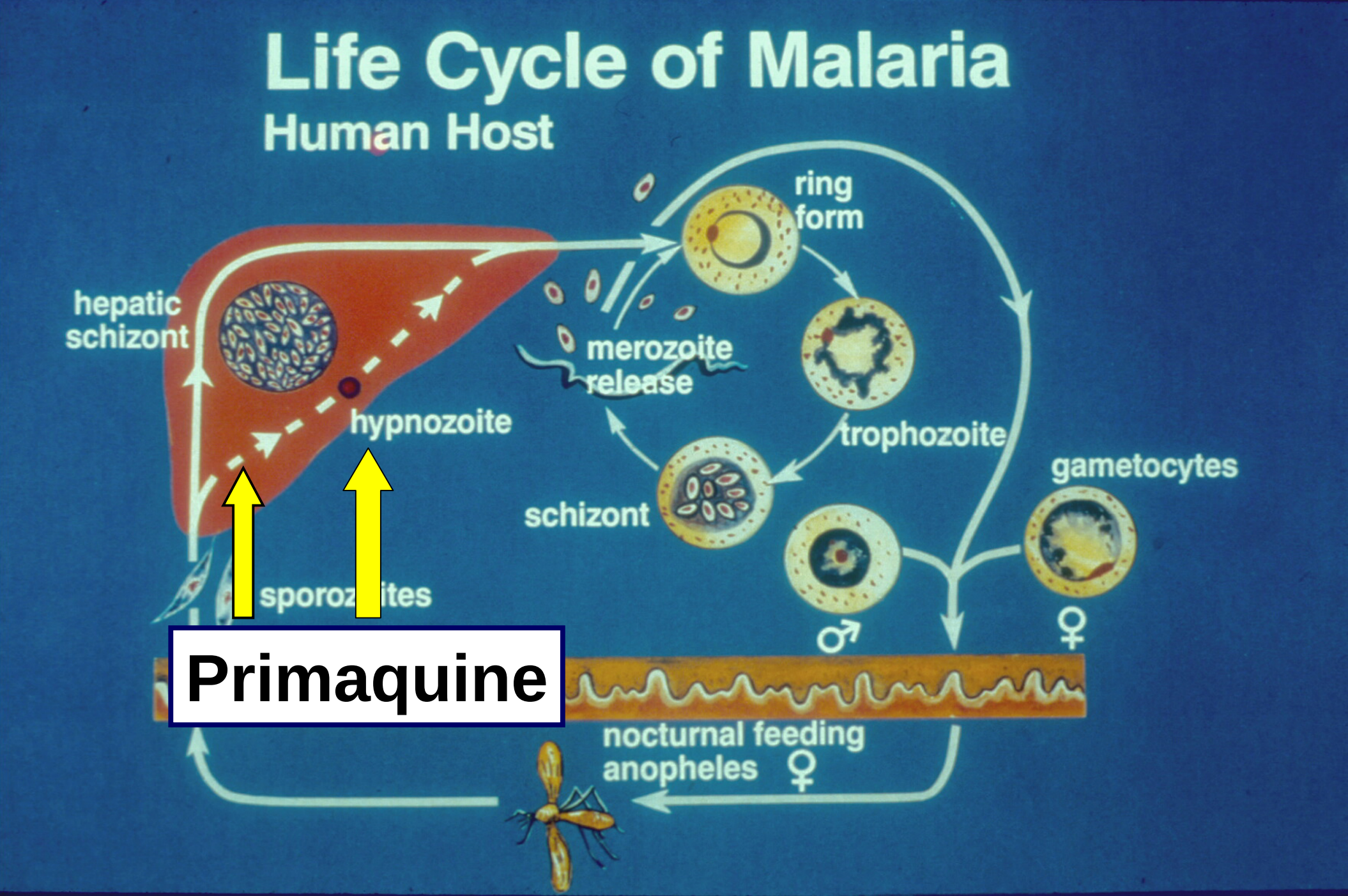
M:F = 4+:1

G6PD deficiency in male US military personnel by WHO level of deficiency.

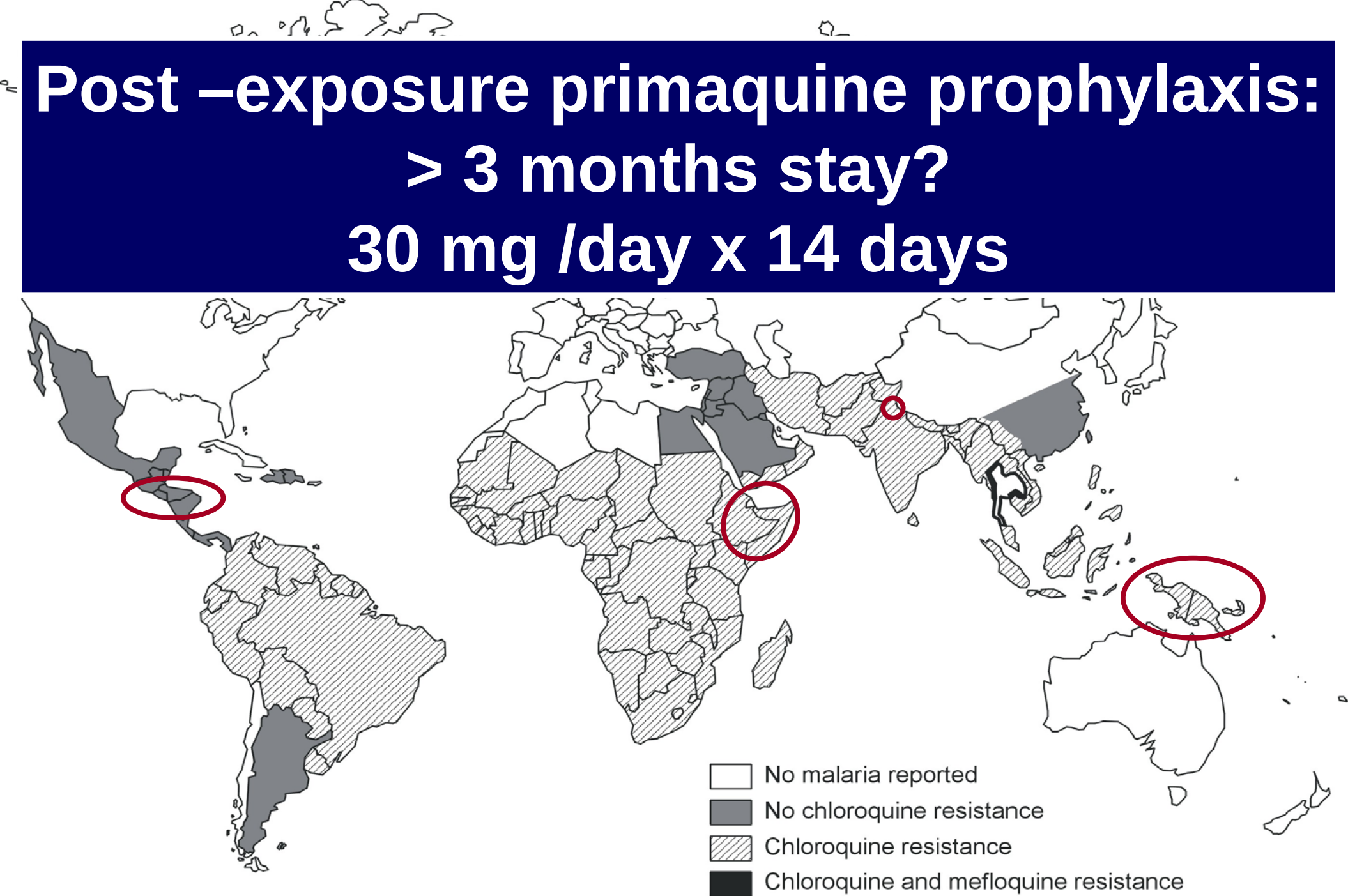


G6PD deficiency in female US military personnel by WHO level of deficiency.




Life Cycle of Malaria
Human Host
ring form
hepatic schizont
merozoite release
hypnozoite
trophozoite
schizont
gametocytes
sporozoites
Primaquine
nocturnal feeding anopheles ♀

Post –exposure primaquine prophylaxis:
> 3 months stay?
30 mg /day x 14 days



Malaria and Pregnancy & Children

Pregnancy:

- CSPF: cloroquine
- CRPF: • mefloquine safe in 2nd trimester, probably 1st

Children:

- Prophylaxis down to age zero

A Randomized Comparison of Artesunate-Atovaquone-Proguanil versus Quinine in Treatment for Uncomplicated Falciparum Malaria during Pregnancy

JID2005;192:846

Rose McGready,[1,2,3] Elizabeth A. Ashley,[1,2,3] Eh Moo,[1] Thein Cho,[1] Marion Barends,[1,2] Robert Hutagalung,[1,2] Sornchai Looareesuwan,[2] Nicholas J. White,[2,3] and François Nosten[1,2,3]

[1]Shoklo Malaria Research Unit, Mae Sot, and [2]Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [3]Centre for Vaccinology and Tropical Medicine, Churchill Hospital, Oxford, United Kingdom

Background. There is no safe, practical, and effective treatment for pregnant women infected with multidrug-

39 women Tx 2nd-3rd trimester
No birth defects @ 1year

interval, 1.7–29.2]; $P = .001$). There were no significant differences in birth weight, duration of gestation, or congenital abnormality rates in newborns or in growth and developmental parameters of infants monitored for 1 year.

3 drugs of choice for Chloroquine Resistance

Drug	Indication
Mefloquine ***Lariam***	**Previous drug use** **Long-stay traveler** **Pregnancy, infancy**
Doxycycline	**Impecunious traveler** **Thai borders**
Atovaquone/proguanil ***Malarone***	**Short-stay traveler** **Drug plan positive** **Thai borders**

Tropical Medicine and International Health

VOLUME 9 NO 12 PP 1241–1246 DECEMBER 2004

Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials

A. M. Dondorp[1,2], P. N. Newton[2,3], M. Mayxay[3], W. Van Damme[4], F. M. Smithuis[5], S. Yeung[1,2], A. Petit[5], A. J. Lynam[6], A. Johnson[7], T. T. Hien[8], R. McGready[1,9], J. J. Farrar[2,10], S. Looareesuwan[1], N. P. J. Day[1,2], M. D. Green[11] and N. J. White[1,2]

21-92% (53%)
in 5 countries of SE Asia

If you take a proven effective antimalarial for chemoprophylaxis

… It works!!

Evaluation of Reported Malaria Chemoprophylactic Failure among Travelers in a US University Exchange Program, 2002

CID 2004;39:1583-8

Louise M. Causer,[1] Scott Filler,[1] Marianna Wilson,[1] Stephen Papagiotas,[2] and Robert D. Newman[1]

[1]Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, and [2]Georgia Division of Public Health, Atlanta, Georgia

5 /25 university students positive smears in Ghana:

↓

malaria antibodies 0/5

(See the e

Backgr ophylaxis and pron 002, we investigat ana and were repo

Metho malaria serologica

Results Disease Control a rence to therapy. T persons reported a aria was performe ggesting that incor

Conclu reports of drug resistance, but it could also result in unnecessary administration of antimalarial treatment. Health care providers and public health authorities must critically evaluate reports of chemoprophylactic failures and disseminate accurate information to travelers.

Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study

Hugh Reyburn, Redempta Mbatia, Chris Drakeley, Ilona Carneiro, Emmanuel Mwakasungula, Ombeni Mwerinde, Kapalala Saganda, John Shao, Andrew Kitua, Raimos Olomi, Brian M Greenwood, Christopher J M Whitty

BMJ 2004;329:1212

Abstract

Objective To study the diagnosis and outcomes in people admitted to hospital with a diagnosis of severe malaria in areas with differing intensities of malaria transmission.

Design Pros… over the cou…

Setting 10 h…

Participants … 4474 (2851 … severe diseas…

Main outcom… outcome. Altitudes of residence (a proxy for transmission intensity) measured with a global positioning system.

Results Blood film microscopy showed that 2062 (46.1%) of people treated for malaria had *Plasmodium falciparum* (slide positive). The proportion of slide positive cases fell with increasing age and increasing altitude of residence. Among 1086 patients aged ≥5 years who lived above 600 metres, only 338 (31.1%) were slide positive, while in children <5 years living in areas of intense transmission (<600 metres) most (958/1392, 68.8%) were slide positive. Among 2375 people who

N=4,450 slides in 10 hospitals

40% false positive blood films

of district hospitals in Africa identified several problems with the organisation and planning of care.[4,5]

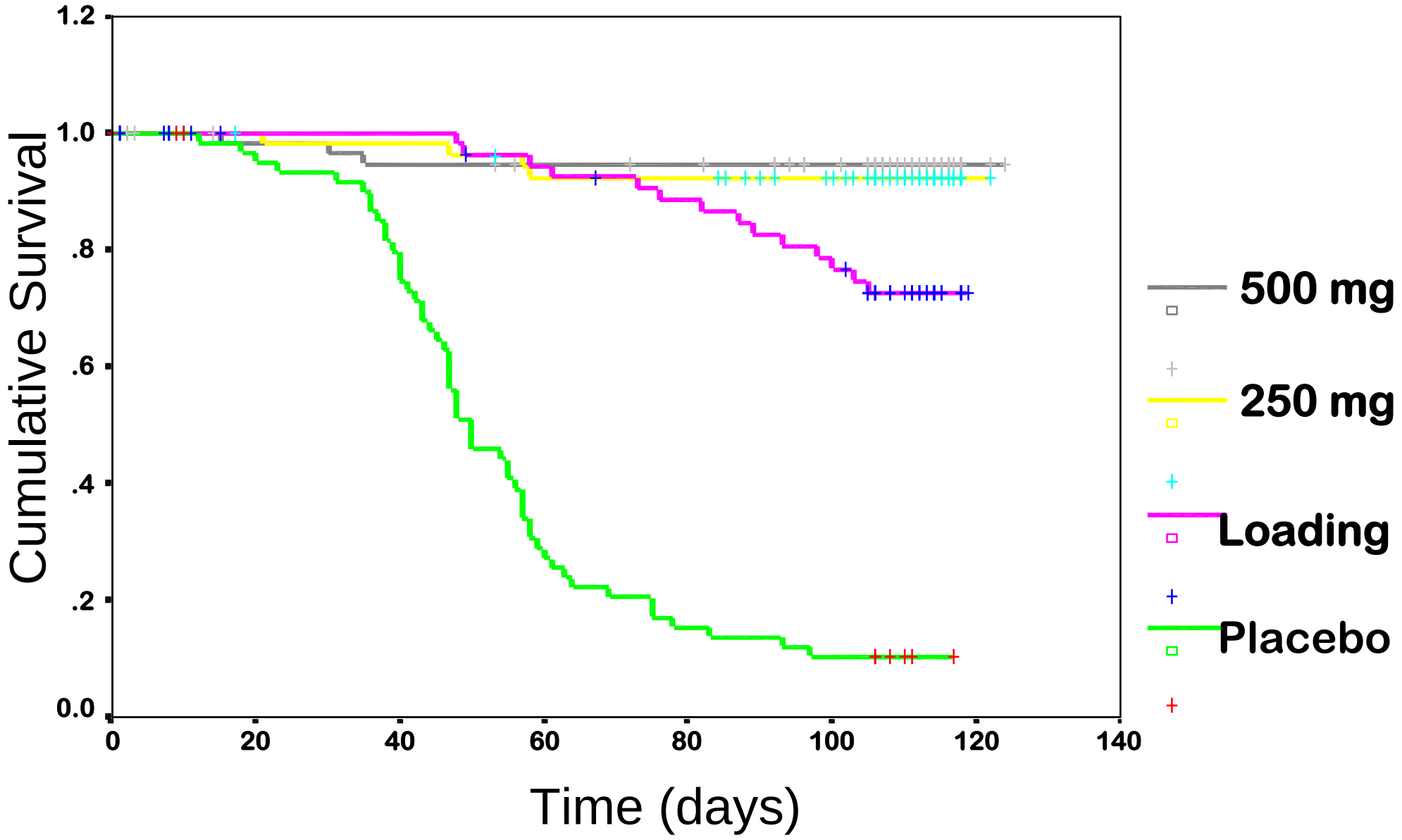
Given the high proportion of admissions attributed to malaria, overdiagnosis of malaria and consequent neglect of alternative diagnoses could lead to avoidable morbidity and …vices with …per health …s such as …to assess. …d to move …roportion of the people treated for malaria do not have the disease this will substantially increase the costs of change.

Accuracy of hospital diagnosis of malaria is likely to depend on the epidemiological probability of the disease (defined by intensity of malaria transmission and age of patients) and is important as most of the population of sub-Saharan Africa live in areas of low or moderate malaria transmission.[7] We prospectively examined the diagnosis and outcome in all patients admitted and treated for severe or potentially complicated malaria during one year in 10 hospitals serving people for areas with

Tafenoquine: New 8-aminoquinoline antimalarial drug

- Primaquine analogue
- approximately 10x efficacy and 1/10 toxicity of primaquine in animal studies
- very long half life (2-4 weeks)
- causes hemolysis in G6PD deficient persons
- apparently kills in both liver and blood

WR238605 Prevention Trial 1997



Malaria morbidity:calculated attack rate per month without chemoprophylaxis

Solomon Is., PNG	> 3%*
West Africa	2.4%
East Africa	1.2%
India	0.35%
SE Asia	0.1%
Latin America:	0.05%

Chemo-prophylaxis

Cutoff Line

Standby medication

Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomised controlled trial

Lancet 2004;364:1411

Pedro L Alonso, Jahit Sacarlal, John J Aponte, Amanda Leach, Eusebio Macete, Jessica Milman, Inacio Mandomando, Bart Spiessens, Caterina Guinovart, Mateu Espasa, Quique Bassat, Pedro Aide, Opokua Ofori-Anyinam, Margarita M Navia, Sabine Corachan, Marc Ceuppens, Marie-Claude Dubois, Marie-Ange Demoitié, Filip Dubovsky, Clara Menéndez, Nadia Tornieporth, W Ripley Ballou, Ricardo Thompson, Joe Cohen

Lancet 2004; 364: 1411–20

See Comment page 1380

Centre de Salut Internacional, Hospital Clínic/IDIBAPS, Universitat de Barcelona

Mozambique (J Sacarlal); (E Macete, I Mandomando,

RCT Mozambique children n=2022

6 mo. PE 1st clin episode: 30%

6 mo. PE severe malaria : 58%

protocol analysis. Vaccine efficacy for the first clinical episodes was 29·9% (95% CI 11·0–44·8; p=0·004). At the end of

group

57·7%

(31·4–55·9; p<0·0001).

Vaccine. 2005 Mar 18;23(17-18):2243-50

Summary Malaria Prevention

- Fever from the tropics is malaria until proven otherwise… and a medical emergency!
- 3 equally effective prevention DOC and 1 alternative (primaquine); start mefloquine 1 mo. before exposure in new patients
- Frequent false positive blood films and counterfeit drugs in the developing world

Summary Malaria Prevention

- No antimalarial is 100% effective…NBce of personal protection measures
- DEET is the most effective & safe insect repellent, including infancy & pregnancy

Travel Medicine for Dummies

- Don’t get bit
- Don’t get hit
- Don’t get lit
- Don’t do “it”
- Don’t eat shit!

David Smith 1986

Further Reading

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